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(54) # PROCESS FOR THE ACYLATION OF 6-AMINOPENICILLANIC (6-APA), 7-AMINOCEPHALOSPORANIC (7-ACA) AND 7-AMINODESACETOXYCEPHALOSPORANIC (7-ADCA) ACIDS AND THEIR DERIVATIVES

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ABSTRACT OF THE DISCLOSURE

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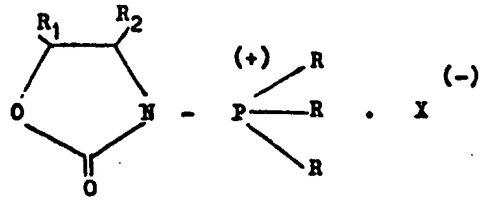
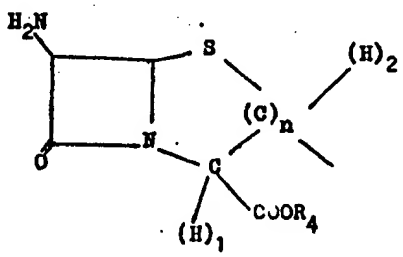
A process for the acylation f 6-aminopenicillanic, amino ephalosporanic, and aminod sacetoxycephalosporanic acids and their derivatives to prepar th corresponding penicillins and cephalosporins. The process comprises reacting in the presence of an inert solvent a compound of the formula:



(I)

where R_1 and R_2 are hydrogen or low molecular weight alkyls, X is an element selected from the halogen group and R is a further group selected from a low molecular weight alkyl, phenyl, halogen and dimethylamin, with a carboxylic acid in the form of a tertiary organic base salt in methylene chloride at temperatures between -15 and +20°C for a period of from 15 to 120 min, to obtain a mixture of active species with a relative proportion of acid halide, N-acyl-2-oxazolidinone and 2-acyloxy-Δ_2-oxazoline, and further reacting the mixture with a solution of a compound of the formula:



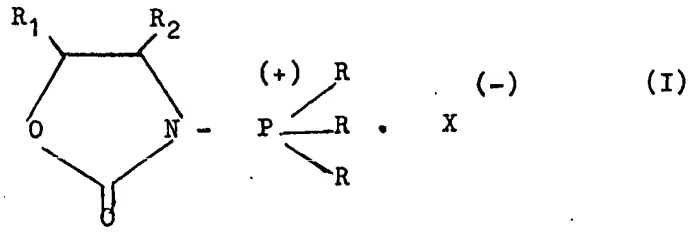
(II)

where n may be 1 or 2, $(H)_2$ may be 0, 2 atoms of hydrogen or a methyl group, $(H)_1$ is O or 1 atom of hydrogen, R_4 an element selected from the group comprising hydrogen, alkali metals, trimethylsilyl, phthalidyl and R_3 selected from the group comprising methyl, azidomethyl, acyloxymethyl, thiolmethyl, 5-methylthiadiazolyl-2-thiomethyl, cyanomethyl, chloromethyl, and methoxymethyl.

The present invention relates to a novel process for the acylation of 6-aminopenicillanic (6-APA), 7-aminocephalosporanic (7-ADCA) acids and their derivatives, such as 7-aminodesacetoxycephalosporanic-3-thio-(2-thiadiazolyl-5-methyl) (7-ACA-TD), 3-pyridimethyl-aminodesacetoxycephalosporanic acid (7-ACA-PYRIDYL) and 6-APA phthalidyl ester, to prepare the corresponding penicillins and cephalosporins.

The process comprises preparing a solution of activated carboxylic acid using as starting products tertiary organic base salts of carboxylic acids, prepared immediately prior to their use. These are made to react with a phosphonium or quasi-phosphonium salt derived from a 2-oxazolidinone. The resulting activated acid solution is reacted with a further solution prepared with an aminopenicillanic or aminocephalosporanic acid, to form respective penicillins or cephalosporins. These are then isolated by known techniques, described in scientific or technical literature, as pharmaceutically applicable acids, esters or non-toxic salts.

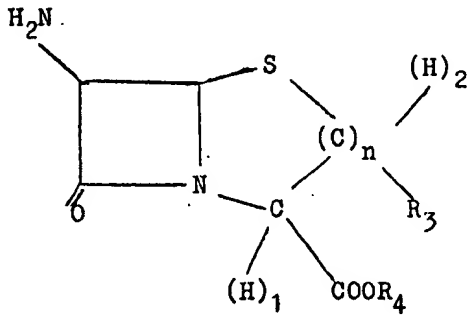
One widespread practical way of conducting the acylation process is related to the preparation of a solution of a carboxylic acid in methylene chloride, by way of an organic base equivalent to give a salt which is added over a suspension or solution of a 3-substituted-2-oxazolidinone having the following formula:



(I)

where R_1 and R_2 are low molecular weight alkyls or hydrogen, X may be an element selected from the halogens and R is a further group selected from among a low molecular weight alkyl, phenyl,

halogen and dimethylamino, which are preferable among others such as diethylamino, diphenylamino, N-morpholino or methylphenylamino. The resulting mixture is reacted with a further solution of a compound selected from the group comprising 6-APA, 7-ACA, 7-ADCA and their derivatives, represented by the following formula:



(II)

where n may be 1 or 2, $(H)_2$ may be 0 or 2 atoms of hydrogen or a methyl group, $(H)_1$ may be 0 or 1 atom of hydrogen, R_4 an element selected from the group comprising hydrogen, alkali metals, trimethylsilyl, phthalidyl and R_3 may represent methyl azidomethyl, acyloxymethyl, thiomethyl, thiadiazolylmethyl, cyanomethyl, chloromethyl, methoxymethyl, to prepare a penicillin or cephalosporin.

Compounds comprising the purpose of the invention and represented by Formula I, that is, the phosphonium or quasi-phosphonium salts, following Kosolapoff and Maier's differential nomenclature (Organic Phosphorous Compounds, Vol. 2 and 6, Wiley Intrs. New York, respectively, page 189-1972 and page 579-1973) are specifically halides of 3-trichlorophosphonium-2-oxazolidinone (CPO), 3-tribromophosphonium-2-oxazolidinone (BPO) and 3-tridimethylaminophosphonium-2-oxazolidinone (HPO) which could also be called phosphoranes, for example, TPO would be chloro-N-oxazolidintriphenylphosphorane. These substances are used in suspension or in solution in an appropriate inert solvent, such as methylene chloride, carbon tetrachloride, chloroform, 1,2-dimethoxyethane, acetonitrile and nitromethane.

The carboxylic acid comprised in the invention may be

selected from the group comprising the aliphatic, alicyclic, aromatic, alkanoaromatic, heterocyclic, alcanoheterocyclic acids and condensated nuclei and dissolved in methylene chloride. Examples of representative acids appropriate for the purposes of the invention are tetrazolyl acetic, cyanacetic, thienyl acetic, pyridincarboxylic, alpha-carboxyindanyl-phenyl acetic acids, derivatives of alpha-carboxy phenyl acetic and alpha-azido phenyl acetic acids, those corresponding to the isoxazolyl-4-carboxylic acid group, a benzoic acid, quinoxaline, etc. and also the organic base may be triethylamine, pyridine, picolines, lutidines, N-ethylpyperidine, N-methylmorpholine, tributylamine, tripropylamine, with the cheapest and most easily obtainable on the market being chosen.

The compounds of Formula II are grouped in a large number of substances having the characteristic of supporting an amino group in their structure. This refers equally to products prepared by semi-synthesis or complete synthesis methods known and described in the literature. The expression "semi-synthesis" is applied when the preparation proceeds directly from penicillins or cephalosporins and the expression "synthesis" is used for those using the fundamental nuclei of 6-APA, 7-ACA and 7-ADCA or their derivatives, such as, e.g., 7-ACA-TD resulting from the reaction between 7-amino-3-methylthiol-Δ_3-cephem-4-carboxylic acid and 2-chloro-5-methyl-thiadiazol, 6-APA-phthalidyl prepared by reacting 6-APA hydrochloride chloride with 2-carboxy benzaldehyde in its hemiacetal cyclic form.

The reaction of an activated acid with CPO, BPO, TPO or HPO and a compound of Formula II, the latter as a triethylamine alkali salt, silyl ester or ester derivative for acylation, is conducted by gradual addition of the acid previously activated with a compound of Formula I over a solution containing an amino-penicillanic or aminocephalosporanic acid at a temperature of from

-15º to +20ºC, with the pH of the medium controlled to from 4 to 6.8, by way of a tertiary organic base or a salt, e.g., a triethylamine salt of acetic, pivalic or 2-ethylhexanoic acid, with the reaction time being extended up to 120 min.

The expression "activated acid" as used in this specification means the reaction between an acid an a compound of Formula I to obtain a solution containing active species which thereafter participate in the acylation process. Some examples of active species were disclosed in Spanish patents nos. 411.867 and 421.660, although it has now been discovered that these species may be controlled with CPO, BPO, TPO and HPO, although the proportion thereof, that is of the acid halides, of N-acyl-2-oxazolidinone and of 2-acyloxy-Δ_2-oxazoline (Δ_2-oxazoline ester), depends on the structure of the reagent and of the acid. It has been possible to prove the presence of these substances by IR spectrography and isolation.

Acid halides are known to be active as acylating agents. The activity of the N-acyl-2-oxazolidinones was disclosed in Spanish patent nº 411.867 and it has now been discovered that Δ_2-oxazoline esters also have this property. It thus happens that the reaction medium between a carboxylic acid salt and a compound of Formula I is constituted by acylating reagents, active species of the carboxylic acid.

For example, the triethylamine salt of 3,5-dinitrobenzoic acid produces an 80% mixture of N-3,5-dinitrobenzoyl-2-oxazolidinone and 2-(3,5-dinitrobenzoyloxy)-Δ_2-oxazoline with CPO, whereas with TPO the oxazoline ester is obtained with virtually quantitative yield. On the other hand, with CPO, thienyl acetic and cyanacetic acid give mainly the acid chlorides and Δ_2-oxazoline esters are produced with alpha-substituted phenyl acetic acids and 3-(O-chlorophenyl)-5-methylisoxazolyl-4-carboxylic acid. Essentially, TPO and HPO cause the formation of Δ_2-oxazoline esters, the presence

of acid chloride being insignificant or non-existent.

These active species may be isolated from the solutions prepared by reacting a carboxylic acid with a compound of Formula I by evaporation of the solvent or precipitation and they may be used in the acylation process. Nevertheless, for the purposes of the invention, it is obviously preferable to use the solution resulting from activation of the acid, without having recourse to further complications caused by isolation and which cause losses. Direct use makes the process more expensive, particularly since mixtures of active species are formed.

The novel acylation process of the invention allows an appropriate Formula I compound to be selected for a particular carboxylic acid and, consequently, it will be hard to find an acid which may not be activated under extraordinarily moderate conditions. In other words it allows a large number of penicillins and cephalosporins to be prepared.

No alteration, decomposition or racemisation phenomena have been observed either with sensitive or optically active acids. Moreover, when Δ_2-oxazoline esters are used, acylation is performed at temperatures from 0º to 20ºC, with the consequent power saving and no additional auxiliary consumption of tertiary organic base is required, since strong inorganic acids are not produced in the reaction medium.

The process is also outstanding with respect to the more stringent requirements for control of impurities in antibiotics particularly impurities coming directly from the products involved in the preparation of penicillins and cephalosporins and which may possibly be harmful for the health. All the compounds resulting from the reaction with CPO, BPO and HPO are water soluble and easily eliminated, like the phosphorous compounds (metabolisable) and 2-oxazolidinone itself, which is harmless. In the case of TPO, the triphenylphosphine oxide is very soluble

in methylene chloride and the sodium salt form of the antibiotic is water soluble, both being easily separable.

All these results may be considered to be surprising in view of the advantages mentioned and of the new active species, Δ_2-oxazoline esters, which cannot be formed by conventional processes.

With a view conveniently to illustrate the description, a series of non-limiting examples are described. Some of these are complemented with the use of isolated Δ_2-oxazoline esters, with a view to showing the effectiveness of these active species produced in the activation of acids in the new acylation process for the preparation of penicillins and cephalosporins. The initials corresponding to the phosphonium halides given in the examples refer to the chloride in the case of CPO and to the bromide in the case of BPO, TPO and HPO. Any other halide is specified, such as HPO chloride or TPO chloride, for example.

EXAMPLES

1. D(-) alpha-azidobenzyl penicillin (Via CPO)

A solution of D(-) alpha-azidophenylacetic acid (20 ml, 2 cmole, 3.543 g) with triethylamine (2 cmole, 2.80 ml) in methylene chloride (20 ml) is added gradually over a suspension of CPO (1 cmole; 2.590 g) in methylene chloride (20 ml) with cooling to -10ºC. Thereafter the mixture is allowed to rise to room temperature while stirring is continued for 120 min. After this time the pH is adjusted to 4 with triethylamine (approximately 1.5 ml).

Thereafter it is poured gradually (30 min) over a further solution prepared from 6-APA (2 cmole; 4.347 g), methylene chloride (30 ml), triethylamine (2 cmole; 2.80 ml), TMSO (3-trimethylsilyl-2-oxazolidinone, 5.0 ml) and pivalic acid (3 cmole; 3.06 g) previously cooled to -15ºC, prior to proceeding to acylation.

The reaction is controlled to from -15° to -10°C during the addition of the activated acid and the pH is adjusted to between 4 and 5 with triethylamine. Thereafter the mixture is stirred for 90 min at 0°C.

The resulting solution is washed with water (15 ml) and HCl is added to pH = 1 (1.5 to 2.0 ml), the organic phase is decanted off, is washed with water and dried with sodium sulphate. Thereafter a solution of sodium 2-ethylhexanoate in MIC (44%; 10 ml) is added and precipitation starts. The resulting mass is diluted with n-heptane at 40°C (400 ml) with good stirring. After 15 min the white product is isolated by filtration, washed with n-heptane and dried to give the sodium salt of the compound of the title (7.34 g; Y = 93% $[\alpha]_D$ = + 180.5° (c = 1%, H_2O). IR spectrum the same as that of a pure sample.

2. Alpha-(n,O-methylphenyl-carbamoyl)-benzyl penicillin (Via CPO)

First phenylmalonic acid hemi-o-toluide (2 cmole; 5.386g) and gradually triethylamine (2 cmole; 2.80 ml) in methylene chloride (20 ml) is added to the CPO (1cmole) suspension prepared according to Example 1. The temperature is then allowed to rise to room temperature (20°C) and stirring is continued for 120 min.

Thereafter the process is conducted in exactly the same way as in Example 1 to give the sodium salt of the compound of the title, a white product (9.40 g; Y = 94%), $[\alpha]_D^{20}$ = + 142.0° (c = 1%, H_2O) with identical IR sepctrum to that of a pure sample.

3. 3(O-chlorophenyl)-5-methyl-4-isoxazolyl penicillin (Via CPO)

Following Example 1, but using 3(O-chlorophenyl)-5-methyl-4-isoxazolylacarboxylic acid (2 cmole; 4.752 g) instead of the D(-) alpha-azidophenyl acetic acid, the pH is adjusted to 5.2-5.5 after 120 min. Dilute in n-heptane and isolate the white precipitate to obtain the sodium salt of the compound of the title

(9.03 g; Y = 96.80%), $[\alpha]_D^{20}$ = + 170.3° (c = 1% in DMSO; crystallised in MIC). The IR spectrum is indentical to that of a pure sample.

4. Alpha-carboxy-5-indanyl bensyl penicillin (Via CPO)

Following Example 2, but using phenylmalonic acid 5-indanyl half ester (2 cmole; 5.928 g) instead of the acid described therein, a solution is produced which is adjusted to pH = 4.9-5.2. This is poured gradually over a further solution of 6-APA prepared as described in Exampel 1. To isolate the penicillin, instead of diluting over n-heptane, isopropanol (250 ml) is added and after removal of the methylene chloride by evaporation at reduced pressure, the mixture is allowed to rest overnight. The white precipitate is filtered and dried to give the sodium salt of the compound of the title (8.29 g; Y = 80%), $[\alpha]_D^{20}$ = + 170.0° (c = 1%, H_2O) with indentical IR spectrum to that of a pure sample.

5. Alpha-carboxyphenyl benzyl penicillin (Via BPO)

Following Example 4 and using monophenyl phenylmalonate (2 cmole; 5.120 g) instead of phenylmalonic 5-indanyl monoester and BPO (1 cmole; 4.360 g) instead of CPO, the resulting mixture from the reaction is washed in water and the organic phase is dried and adjusted to pH = 6 with sodium 2-ethylhexanoate. It is then concentrated at reduced pressure and diluted with n-heptane. The white precipitate is filtered and dried to give the sodium salt of the compound of the title with almost quantitative yield (9.20 g). The IR spectrum is indentical to that of a pure sample.

6. 7-(phenoxyacetamido)-desacetoxycephalosporanic acid (Via BPO)

A solution of phenoxyacetic acid (3 cmole; 4.560 g) with N-methylmorpholine (3 cmole; 3.033 g) in methylene chloride

(20 ml) is added gradually to a suspension of BPO (1.5 cmole; 6.540 g) in methylene chloride (50 ml) with cooling to -15°C. The temperature is then allowed to rise to room temperature and stirring is continued for 120 min. After adjusting to pH = 4 with methylmorpholine, the solution is added over a further trimethylsilyl ester solution prepared with 7-ADCA (3 cmole; 6.429 g) in methylene chloride (30 ml). Thereafter acetic acid (2.25 ml) and triethylamine (4.2 ml) in methylene chloride (10 ml) is added and stirring is continued for 60 min, at a temperature of from 0° to 5°C. Then 20 ml water are poured in and the mixture is adjusted to pH = 1 with HCl. The organic phase is decanted off, washed three times with water and then dried with sodium sulphate anhydride. It is then concentrated at reduced pressure, ethyl acetate (25 ml) is added to the resulting solution which is then concentrated to produce crystallisation. The compound of the title is isolated by filtration with a virtually quantitative yield (9.409 g), m.p. = 170-184°C; recrystallised in ethyl acetate, m.p. = 184-6°C. IR spectrum identical to that of a pure sample.

7. 7-(alpha-chlorophenylacetamido)-cephalosporanic acid (Via BPO)

Follow Example 6, but using a solution of alpha-chlorophenylacetic acid (1 cmole; 1.705 g) and N-ethylpiperidine (1 cmole; 1.132 g) in methylene chloride (10 ml) and a suspension of BPO (0.5 cmole; 2.180 g) in carbon tetrachloride (20 ml). Then replace the 7-ADCA trimethylsilyl ester with 7-ACA (1 cmole; 3.040 g) in methylene chloride (30 ml), the reaction being conducted in a similar way. After washing with water and drying, concentrate at reduced pressure and the residue is diluted with n-heptane until it turns turbid, whereafter it is allowed to rest for crystallisation. The compound of the title is isolated (4.00 g; Y = 87.6%), m.p. = 88-90°C. Neutralisation equivalent: calculated 424.5; found: 415; IR spectrum identical to that of a pure sample.

8. 7-(alpha-chlorophenylacetamido)-desacetoxycephalosporanic acid (Via BPO)

Follow Example 6 but use alpha-chlorophenylacetic acid (3 cmole; 5.115 g) and tributylamine (3 cmole; 5.560 g) instead of the phenoxyacetic acid and N-methylmorpholine, respectively. The organic phase is isolated, washed and extracted with water (90 ml), ammonium hydroxide is added to give an alkaline pH to phenolphthalein. The water phase is drawn off and treated with HCl to give a white solid which, when filtered and dried, gives the compound of the title (9.900 g; Y = 86.4%), m.p. = 152-4°C. Neutralization equivalent, calculated: 366.5; found: 367. IR spectrum equivalent to that of a pure sample.

9. 7-(1-(1H)-tetrazolylacetamido)-cephalosporanic acid sodium salt (Via CPO)

The reaction is conducted in a similar way to Example 6, with CPO (1.5 cmole; 3.885 g), 1-(1H)-tetrazolyl acetic acid (3 cmole; 3.840 g), beta-picoline (3 cmole; 2.700 g) and 7-ACA (3cmole; 9.120 g) instead of BPO, phenoxyacetic acid, N-methylmorpholine and 7-ADCA, respectively. The mixture resulting from the operation is diluted with an equal volume of isopropanol and 100 ml water, followed by adjustment to pH = 2.2. The organic phase is decanted off and the methylene chloride is evaporated at reduced pressure. After concentration a sodium 2-ethylhexanoate solution is added. The white precipitate is filtered, washed with isopropanol-water (80%) and dried to give the compound of the title (11.17 g; Y = 90.0%), m.p. = 175-9°C (d). IR spectrum identical to that of a pure sample.

10. 7-(1-(1H)-tetrazolylacetamido)-3-(5-methyl-1,3,4-thiadiazolyl-2-thiomethyl)-Δ_3-cephem-4-carboxylic acid (Via CPO)

A solution of 1-(1H)-tetrazolylacetic acid (3 cmole; 3.840 g) and triethylamine (3 cmoles; 4.20 ml) in methylene chloride (60 ml) is added quickly with good stirring to a suspension of CPO (1.5 cmoles; 3.885 g) in methylene chloride (60 ml) at -15ºC. After 60 min at 25ºC it is added gradually over a further solution, chilled in an ice-water bath, of 7-ACA-TD (3 cmoles; 10.333 g) (7-amino-3-(5-methyl-1,3,4-thiadiazolyl-2-thiomethyl)-Δ_3-cephem-4-carboxylic acid) as trimethylsilyl ester (prepared with 3-trimethylsilyl-2-oxazolidinone) in methylene chloride (60 ml). Stirring is continued for 60 min and the evolution of the reaction is controlled by adjusting to pH = 4 with a triethylamine pivalate solution. The resulting mixture is washed with a sodium chloride solution and then extracted with water and sodium hydroxide, the water phase being drawn off. The water phase is chilled in an ice-water bath, HCl is added and the white precipitate is filtered, washed and dried to give the compound of the title (12.00 g; Y = 88.0%), on recrystallisation has m.p. = 196-9ºC(d) and IR spectrum identical to that of a pure sample.

The 7-ACA-TD was prepared by heating a solution of 7-(alpha-chlorophenylacetamido)-3-thiomethyl-Δ_3-cephem-4-carboxylic acid trimethylsilyl ester (3 cmoles; 11.960 g), 2-chloro-5-methyl-thiadiazol (3 cmoles; 4.035 g) in dimethylformamide with pH adjusted with quinolein to 70ºC. The 7-ACA-TD group was then released with thiourea, following the process described in Spanish patent nº 431.484.

11. 7-(thienylacetamido)-cephalosporanic acid (Via CPO)

Following Example 9 and using thienylacetic acid (3 cmoles; 4.323 g) instead of the tetrazolylacetic acid, evaporation of the solvent gives a precipitate which, after isolation by filtration, gives the compound of the title (10.20 g; Y = 85.2%) identified by IR spectrum, identical to that of a pure sample; m.p.

169-172°C (d).

12. 7-(thienylacetamido)-3-pyridylmethyl)-Δ_3-cephem-4-carboxylate (Via CPO)

Thienylacetic acid (1 cmole; 1.442 g) is activated with CPO (0,5 cmole) according to Example 11. Thereafter it is added over 7-ACA-pyrimidyl (1 cmole; 2.913 g) (7-amino-3-pyridyl-methyl)-Δ_3-cephem-4-carboxylate) in methylene chloride (30 ml) with stirring in an ice bath and with pH controlled to 5. After 60 minutes the solvent is removed by evaporation and the residue is treated first with moist methylisobutylketone and then with water (7ml) and then left to crystallise in an ice bath. The precipitate is filtered and dried and the treatment is repeated with the mother liquor, to give the compound of the title (3.05 g; Y = 73.2%) identified by its IR sepctrum, identical to that of a pure sample. Optical activity +47.0° (c =1%, H_2O).

13. 7-(3,5-dinitrobenzoylamido)-3-azidomethyl-Δ_3-cephem-4-carboxylic acid. (Via TPO)

A solution of 3,5-dinitrobenzoic acid (1 cmole; 2.121 g) and triethylamine (1 cmole; 1.42 ml) in methylene chloride (10 ml) is added over a further solution of TPO (1 cmole; 4.282 g) in methylene chloride (20 ml) with cooling in an ice water bath. After stirring for 15 min, it is added over 7-amino-3-azidomethyl-Δ_3-cephem-4-carboxylic acid trimethylsilyl ester, prepared with the 3-azido derivative of 7-ADCA (1 cmole; 2.552 g), 3-trimethylsilyl-2-oxazolidinone (2.5 ml) in methylene chloride (20 ml) with adjustement to pH = 6 with triethylamine acetate. The mixture is stirred at room temperature (20°C) for 30 min. The resulting solution is adjusted to pH = 2 and washed with water (10 ml) several times, the organic phase is then extracted with more water (10 ml) and ammonium hydroxide until the pH is alkaline with phenolphthalein. The

aqueous liquors are cooled in an ice bath and precipitated with dilute HCl. The product is filtered and dried to give the compound of the title (4.10 g; Y = 91.2%); identified by its IR spectrum with characteristic bands due to the beta-lactam nucleus and the azido and nitro functions in the usual positions.

14. 7-(3,5-dinitrobenzoylamino)-desacetoxycephalosporanic acid. (Via 2-(3,5-dinitrobenzoyloxy)-Δ_2-oxazoline).

First triethylamine pivalate (0.5 cmole; 0.545 g pivalic acid and 0.70 ml base) and thereafter 2-(3,5-dinitrobenzoyloxy)-Δ_2-oxazoline (1 cmole; 2.812 g) prepared from CPO and 3,5-dinitrobenzoic acid 2,4-lutidine salt is added to a solution of 7-ADCA (1 cmole; 2.142 g) prepared in methylene chloride (30 ml) in the trimethylsilyl ester form. After 15 min stirring at 20°C, water is added, the organic phase is decanted off and extracted with an ammonium hydride aqueous solution. This is cooled and the compound of the title (3.074 g; Y = 75.3%) is precipitated out with HCl. It is identified by its IR sepctrum and shows the corresponding bands due to the beta-lactam nucleus and nitro groups.

15. 6[3-(2,6-dichlorophenyl)-5-methylisoxazolyl-4-carboxyamido]-penicillanic acid sodium salt. (Via 2[3-(2,6-dichlorophenyl)-5-methylisoxazolyl-4-carbonyloxy]-Δ_2-oxazoline).

A solution of 6-APA (1 cmole; 2.162 g) trimethylsilyl ester is prepared in methylene chloride (10 ml) with triethylamine (1 cmole; 1.40 ml) and 3-trimethylsilyl-2-oxazolidinone (2.0 ml). Then pivalic acid (1 cmole; 1.10 g) followed by the Δ_2-oxazoline ester of the title (1 cmole; 3.411 g) are added. The mixture is stirred for 15 min at 20°C. The resulting solution is first washed with water, then adjusted to pH = 2, the organic phase is decanted off, dried and adjusted to pH = 6.5 (4 to 5 ml of a 44% sodium 2-ethylhexanoate solution in methylisobutylketone). After concentration

at reduced pressure, the liquors are first diluted with isopropanol and then with n-heptane (200 ml) to produce a white precipitate which is isolated and washed. Once dry it gives the compound of the title with an almost quantitative yield (4.770 g). The optical activity is +134º (c = 1%, H_2O), crystallised from methylisobutyl-ketone, it has m.p. 212-214ºC (d) and IR sepctrum identical to that of a pure sample.

The Δ_2-oxazoline ester isolated from the reaction between HPO and the acid triethylamine salt has m.p. 209-211ºC and characteristic readings in IR with intense bands at 1785 cm^{-1} and 1728 cm^{-1} (BrK).

16. 6[3-(2-chlorophenyl)-5-methylisoxazolyl-4-carboxyamido]- penicillanic acid sodium salt. (Via 2[3-(2-chlorophenyl)-5-methylisoxazolyl-4-carbonyloxy]-Δ_2-oxazoline).

Operating in a similar way to Example 15 and replacing the Δ_2-oxazoline ester with the corresponding ester of the title (1 cmole; 3.066 g), the penicillin is produced with comparable yield. In IR it has a spectrum identical to that of a pure sample. The Δ_2-oxazoline ester, with m.p. 115-119ºC, gives intense IR spectrum readings at 1795 cm^{-1} and 1730cm^{-1} (BrK).

17. 6[3-(2-fluor-5-chlorophenyl)-5-methylisoxazolyl-4-carboxyamido]-penicillanic acid sodium salt. (Via 2[3-(2-fluor-6-chlorophenyl)-5-methylisoxazol-4-carbonyloxy]-Δ_2-oxazoline).

Operating in a similar way to Example 15 and replacing the Δ_2-oxazoline ester with the corresponding ester of the title (1 cmole; 3.247 g), the penicillin is produced with comparable yield. In IR it has a spectrum identical to that of a pure sample. The Δ_2-oxazoline ester gives intense IR spectrum readings at 1795 cm^{-1} and 1729 cm^{-1} (BrK).

18. 7[1-(1H)-tetrazolylacetamido]-3-(5-methyl-1,3,4-thiadiazolyl-2-

thiomethyl)-Δ_3-cephem-4-carboxylic acid sodium salt. (Via 2[1-(1H)-tetrazolylacetyloxy]-Δ_2-oxazoline).

A solution of 7-ACA-TD (3 cmoles; 10.332 g) is prepared in water (50 ml) and sodium hydroxide is added until the solution is alkaline to phenolphthalein. Thereafter ethanol (50 ml) and the Δ_2-oxazoline ester of the title (3 cmoles; 5.916 g) are added. The mixture is held with good stirring at a temperature of 10°C for 30 min and then mixed with further ethanol (75 ml) and allowed to crystallise in ice bath. The white precipitate produced is filtered, washed with ethanol and dried to give the compound of the title (10.75 g; Y = 75.1%) m.p. 185°C and IR spectrum identical to that of a pure sample. The Δ_2-oxazoline ester gives characteristic intense IR readings at 1800 cm^{-1} and 1730 cm^{-1} (BrK).

19. 7-(cyanacetamido)-cephalosporanic acid sodium salt. (Via 2-(cyanacetiloxy)-Δ_2-oxazoline).

Following Example 18 and replacing the 7-ACA-TD with 7-ACA (3 cmoles; 8.166 g), the ethanol with isopropanol and the Δ_2-oxazoline ester with the corresponding ester of the title (3 cmoles; 4.623 g) and operating in a similar way, the compound of the title is isolated with a comparable yield. The IR spectrum gives an identical reading to that of a pure sample. The liquid Δ_2-oxazoline ester gives characteristic IR readings at 1798 cm^{-1} and 1732 cm^{-1}, apart from the one due to the nitrilo group.

20. 7-(3,5-dinitrobenzoylamido)-3-methylthiol-Δ_3-cephem-4- carboxylic acid. (Via 2-(3,5-dinitrobenzoyloxy)-Δ_2-oxazoline ester).

Following Example 14 and replacing the 7-ADCA with 7-amino-3-methylthiol-Δ_3-cephem-4-carboxylic acid (1 cmole; 2.463 g), the compound of the title is isolated with comparable yield. Identified by its IR spectrum. The Δ_2-oxazoline ester has m.p. 216°C and

gives intense characteristic readings in IR at 1805 cm^{-1} and 1745 cm^{-1} (KBr), as well as those corresponding to the nitro group.

The 7-amino-3-thiomethyl-Δ_3-cephem-4-carboxylic acid was prepared either by reaction of the corresponding chloromethyl derivative and sodium monosulphide solution in dimethylformamide solution or, alternatively, by treatment of 7-(alpha-chlorophenylacetamido)-3-chloromethyl-Δ_3-cephem-4-carboxylic acid in acetonitrile with thiourea, as described in Spanish patent nº 431.585, with release of the corresponding thiomethyl derivative.

21. 7-(alpha-bromophenylacetamido)-3-chloromethyl-Δ_3-cephem-4-carboxylic acid. (Via HPO chloride)

Operate in a similar way to Example 13 replacing the 3,5-dinitrobenzoic acid with alpha-bromophenylacetic acid (1 cmole; 2.150 G), the TPO with HPO chloride (1 cmole; 2.847 g) and the 7-amino-3-azidomethyl-Δ_3-cephem-4-carboxylic acid with the corresponding 3-chloromethyl derivative (1 cmole; 2.487 g). Isolation conducts to the compound of the title (3.660 g; Y = 82.1%), identified by its IR spectrum, neutralisation equivalent and iodometric evaluation, with 98.2% purity.

22. 7-(cyclohexylcarboxyamido)-3-methoxymethyl-Δ_3-cephem-4-carboxylic acid. (Via 3-trisdimethylaminophosphonium-4-methyl-2-oxazolidinone (HPO-4-methyl) bromide).

Operating in a similar way to Example 13 and replacing the 3,5-dinitrobenzoic acid with cyclohexanecarboxylic acid (1 cmole; 1.281 g), the TPO with HPO-4-methyl (1 cmole; 3.431 g) and the azidomethylcephalosporanic acid with 7-amino-3-methoxymethyl-Δ_3-cephem-4-carboxylic acid (1 cmole; 2.442 g), the compound of the title is produced (2.481 g; Y = 70.0%) identified by its IR spectrum and beta lactam nucleus. Iodometric evaluation shows it to be 94.3% pure.

23. 7-(quinoxalin-2-carboxyamido)-3-cyanomethyl-Δ_3-cephem-4-carboxylic acid. (Via 3-trisdimethylaminophosphonium-5- methyl-2-oxazolidinone chloride (HPO-5-methyl chloride).

Following Example 6 and replacing the BPO with HPO-5-methyl chloride (1 cmole; 2.987 g), the phenoxyacetic acid with quinoxalin-2-carboxylic acid (1 cmole; 1.741 g) and the 7-ADCA with 7-amino-3-cyanomethyl-Δ_3-cephem-4-carboxylic acid, the result is the compound of the title with almost quantitative yield (3.954 g). Identified by its IR sepctrum, beta lactam nucleus and nitrilo group; neutralisation equivalent and iodometric evaluation (more time than usual required during treatment with alkali - 90 min).

24. 6-(pyridin-3-carboxyamido)-penicillanic acid phthalidyl ester. (Via 3-trichlorophosphonium-4-methyl-2-oxazolidinone chloride (CPO-4-methyl).

Nicotinic acid (1 cmole; 1.231 g) is treated with CPO-4-methyl (0.5 cmole; 1.415 g) in a similar way to Example 1, followed by gradual addition over 6-aminopenicillanic acid phthalidyl ester (1 cmole; isolated from hydrochloride, 3.848 g) in 40 ml methylene chloride with the temperature controlled by ice bath. After 60 min stirring, water (10 ml) is added, pH is adjusted to 6, the organic phase is decanted off, washed with water, dried and concentrated at reduced pressure. Thereafter the mixture is saturated with hydrogen chloride, diluted with n-heptane and left in the refrigerator. The product, filtered and washed with n-heptane and dried, gives the compound of the title as the hydrochloride (4.223 g; Y = 80.3%). Identified by Its IR spectrum with the characteristic bands corresponding to the beta-lactam nucleus, aromatic and pyridine nucleus; iodometric evaluation - 94.6% and bioassay 895 µg/g.

The 6-APA phthalidyl ester was prepared by reacting 6-APA hydrochloride chloride (2 cmole; 5.438 g) in methylene chloride

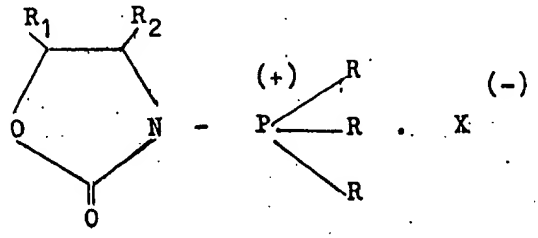
(40 ml) with 2-carboxybenzaldehyde cyclic hemiacetal (2.5 cmole; 3.753 g) with stirring in a water-ice bath for 120 min. Thereafter the product was filtered and dried. The purity was evaluated with standardised sodium hydroxide solution.

25. 6-(5-nitrofuryl-2-carboxyamido)-penicillanic acid sodium salt. (Via 3-trichlorophosphonium-4,5-dimethyl-2-oxazolidinone chloride (CPO-4,5-dimethyl).

Following Example 1 exactly and replacing the CPO with CPO-4,5-dimethyl (1 cmole; 3.070 g), the alpha-azidophenylacetic acid with 5-nitro-2-furoic acid (2 cmoles; 3.141 g) and the triethylamine with pyridine, the result is the compound of the title (7.409 g; Y = 98.2%). Characterised by the IR spectrum bands and thin layer chromatography (developed with a concentrated NaOH solution in methanol-acetone), with identical Rf to that of a pure sample.

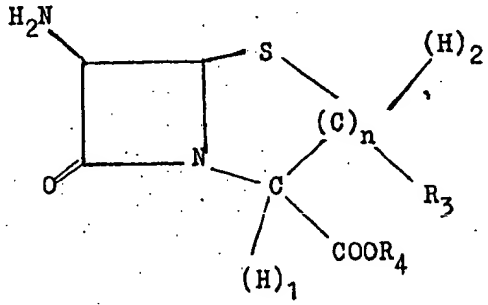
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for the acylation of aminopenicillanic, aminocephalosporanic, and aminodesacetoxycephalosporanic acids and their derivatives, characterised in that a compound of the following formula:



(I)

where R_1 and R_2 are hydrogen or low molecular weight alkyls, X may be an element selected from the halogen group and R is a further group selected from a low molecular weight alkyl, phenyl, halogen and dimethylamin, is reacted with a carboxylic acid in the form of a tertiary organic base salt in methylene chloride at temperatures between -15 and +20°C for a period of from 15 to 120 min, to obtain a mixture of active species with a relative proportion of acid halide, N-acyl-2-oxazolidinone and 2-acyloxy-Δ_2-oxazoline, and further reacting the mixture in an inert solvent with a compound of the following formula :



(II)

where n may be 1 or 2, $(H)_2$ may be 0, 2 atoms of hydrogen or a methyl group, $(H)_1$ is 0 or 1 atom of hydrogen, R_4 an element selected from the group comprising hydrogen, alkali metals, trimethylsilyl,

phthalidyl and R_3 selected from the group comprising methyl, azidomethyl, acyloxymethyl, thiolmethyl, 5-methylthiadiazolyl-2-thiomethyl, cyanomethyl, chloromethyl, methoxymethyl, to prepare a penicillin or cephalosporin.

2. A process according to claim 1, wherein a compound of Formula I, where R_1 and R_2 are hydrogen, X and R have the meaning given above, is reacted in an inert solvent with a carboxylic acid salt, selected from the group comprising aliphatic, alicyclic, aromatic, alkanoaromatic, heterocyclic, alkanoheterocyclic acids and condensed nuclei, with tertiary organic bases of the group comprising pyridine, picolines, lutidines, triethylamine, tributylamine, N-ethyl piperidine and N-methylmorpholine and the resulting mixture is made to react with a further solution of compound II in methylene chloride to obtain a penicillin or cephalosporin.

3. A process according to claim 1, wherein a compound of Formula I where R_1 and R_2 are hydrogen, X and R have the meaning given above, is made to react in an inert solvent with a tertiary organic base salt and carboxylic acid, the acid being selected from the group comprising benzoic, phenylacetic, acetic, pyridincarboxylic, quinoxalincarboxylic, isoxazolylcarboxylic acids and the resulting mixture is reacted with a further solution of a compound of formula II in methylene chloride to obtain a penicillin or cephalosporin.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente